IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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Inventors:	**Hamilton and Stanton**
Serial No.:	**10/089,475**
Filing Date:	**August 12, 2002**
Examiner:	**Pak, Michael D.**
Customer No.:	**26259**
Group Art Unit:	**1646**
Confirmation No.:	**1040**
Title:	**Compositions and Methods for Modulating ATP-Binding Cassette Transmembrane Reporter Protein Expression**

Electronically Submitted via EFS-Web
Date: **November 27, 2007**

I hereby certify that this paper is being electronically submitted on the date indicated above to the Commissioner for Patents, U.S. Patent & Trademark Office (AF).

By _____
Typed Name: **Jane Massey Licata, Reg. No. 32,257**

Commissioner for Patents
U.S. Patent & Trademark Office
(AF)

APPEAL BRIEF

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I. Real Party in Interest

The real party in interest is Trustees of Dartmouth College.

II. Related Appeals and Interferences

There are no related appeals or interferences.

III. Status of Claims

Claim 9 is pending in this application.

Claims 1-8 and 10-11 have been canceled.

Claim 9 has been rejected and is on appeal. A claim appendix including the text of the appealed claim is attached.

IV. Status of Amendments

The response to the Final Office Action filed on August 8, 2007 was entered upon filing of this appeal. However, an October 16, 2007 Advisory Action indicated that the rejections were maintained.

V. Summary of the Claimed Subject Matter

Claim 9 defines a method for identifying agents which increase functional cell surface expression of a mutant cystic fibrosis transmembrane conductance regulator (CFTR) protein. See page 3, (lines 25-27), the sentence bridging pages 4-5, page 5 (lines 25-29), page 6 (lines 9-13), page 7 (lines 31-33) and page 8 (lines 1-6).

The method of the invention employs cells transfected with a genetic construct composed of a cDNA encoding a mutant human CFTR protein having a deletion of the phenylalanine at amino acid position 508 (ΔF508). See page 3 (lines 29-30), the sentence bridging pages 3-4, page 5 (lines 14-25), page 6 (lines 13-16), and page 6 (lines 21-22),

The genetic construct of the claimed invention further includes a cDNA of an EGFP reporter gene linked at the 5′ end to

the cDNA encoding the mutant human CFTR protein. See the sentence bridging pages 3-4, page 5 (lines 14-25), page 6 (lines 13-16), the paragraph spanning pages 5 and 6.

Moreover, the expression of the cDNAs of the genetic construct of the instant claim are under the regulation of the proximal human CFTR promoter region. See the sentence bridging pages 3-4, page 5 (lines 21-25), and page 6 (lines 13-18).

Supporting disclosure for introducing and expressing the genetic construct in cells is found at page 7 (lines 15-23).

In accordance with the present claim, cells transfected with the genetic construct are exposed to an agent. See the sentence bridging pages 3-4 and page 8 (lines 1-6). Subsequently, CFTR expression or activity levels or trafficking of CFTR to the cell membrane in the exposed cells is measured. See page 5 (lines 2-4) and page 6 (lines 24-28). Measured CFTR expression levels or activity or trafficking of CFTR to the cell membrane in the exposed cells are then to CFTR expression or activity levels or trafficking of CFTR to the cell membrane in cells not exposed to the agent, wherein an increase in CFTR expression or activity levels or trafficking of CFTR to the cell membrane in the exposed cells as compared to the unexposed cells is indicative of the agent being useful in increasing functional cell surface expression of a ΔF508 mutant CFTR protein. See page 5 (lines 4-11) and the paragraph bridging pages 7-8. Exemplification of the instant method is found in the passage at page 8 (line 34) to page 10 (line 34).

VI. Grounds of Rejection to be Reviewed on Appeal

Whether claim 9 should stand rejected under 35 U.S.C. §112, second paragraph, as being indefinite for reciting "ΔF508 mutant".

Whether claim 9 should stand rejected under 35 U.S.C. §103(a) as being obvious over the Moyer et al. in view of Cormack and Chou et al.

VII. Arguments

A. The Rejection of Claim 9 Under 35 U.S.C. §112, Second Paragraph Should Be Withdrawn

MPEP 2173.02 states that the essential inquiry pertaining to whether a claim is indefinite is whether the claims set out and circumscribe a particular subject matter with a reasonable degree of clarity and particularity. Definiteness of claim language must be analyzed, not in a vacuum, but in light of:

(A) The content of the particular application disclosure;

(B) The teachings of the prior art; and

(C) The claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made.

The specification at page 3, lines 15-18, teaches that a single mutation resulting in a deletion of the phenylalanine at position 508 of the CFTR protein, known as ΔF508, accounts for approximately 67% of mutation in all CF patients. Indeed, this mutation is generally well-known in the art. For example, Wikipedia indicates that "[t]he most common mutation, called ΔF508, is a deletion (Δ) of one amino acid at position 508 in the CFTR protein." See attached definition of CFTR (Appendix B.1). In fact, the ΔF508 mutation has its own entry in Wikipedia, defined as:

> "a specific mutation within the human genome. The mutation--a deletion of three base pairs (A, T, T) which form the codon for phenylalanine (F) at the 508 position--prevents a protein called the cystic fibrosis transmembrane conductance regulator (CFTR) from obtaining its normal position. Having two copies of this mutation, inherited from both parents, is the leading cause of cystic fibrosis (CF)." See enclosed definition of ΔF508 (Appendix B.2).

In addition to this general reference to ΔF508 CFTR, pages 88-89 of A Dictionary of Genetics (enclosed herewith as Appendix B.3) indicates that the ΔF508 mutation is present in 60-70% of the CF

chromosomes from North American Caucasians and results in a temperature sensitive defect in protein processing.

As currently presented, claim 9 reads on a cDNA encoding a mutant human CFTR protein having a deletion of the phenylalanine at amino acid position 508 (ΔF508). In a search of the ENTREZ GENE database at NCBI (www.ncbi.nlm.nih.gov), only one mRNA is listed as encoding human CFTR (*i.e.*, NM_000492.3; enclosed herewith as Appendix B.4). Likewise, only one accession number is listed for the human CFTR protein (*i.e.*, NP_000483.3; enclosed herewith as Appendix B.5). See also ENTREZ GENE record for CFTR cystic fibrosis transmembrane conductance regulator (ATP-binding cassette sub-family C, member 7) [*Homo sapiens*], enclosed herewith (Appendix B.6). In both cases, *i.e.*, the deduced protein sequence of the mRNA of Accession No. NM_000492.3 and the protein of Accession No. NP_000483.3, a phenylalanine is found at position 508. See attached GENBANK entries. As such, it would be readily clear which phenylalanine of human CFTR is being referred to in the present claim.

Appellants further note that numerous scientific references and patents discuss human ΔF508 CFTR. Indeed, a search of the NCBI PUBMED database for the keywords "human", "deltaF508", and "CFTR" identifies approximately 420 hits. Moreover, Appellants have directed the Examiner's attention to claims 1 and 4 of U.S. Patent No. 6,902,907 (filed June 2, 1994), which read on a F508 mutation which comprises a three base pair deletion of a DNA sequence encoding a phenylalanine corresponding to amino acid position 508 of a normal CFTR protein. In this regard, it is accepted in the art that a ΔF508 mutant of human CFTR is a deletion of the phenylalanine at position 508 of the well-known CFTR protein.

Therefore, based upon the disclosure in the instant specification, the teachings of the prior art, and the claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was

made, Appellants submit that the skilled artisan would find the phrase "ΔF508 mutant" to be clear and definite as used in the presently pending claim.

B. The Rejections of Claim 9 Under 35 U.S.C. §103(a) in View of Moyer et al., Cormack, and Chou et al. Should Be Withdrawn

The Examiner suggests that Moyer et al. teach a method of measuring the effect of butyrate on expression of a CFTR-GFP nucleic acid and Cormack et al. teach mutants of GFP which fluoresce more intensely than wild-type GFP. It is further suggested that Chou et al. teach transcriptional regulatory elements of CFTR. The Examiner asserts that because the metes and bound of "ΔF508 mutant human CFTR cDNA coding region" is not clear, the CFTR-GFP nucleic acid of Moyer et al. meets the limitation of the mutant human CFTR of the present claims. See the paragraph bridging pages 3 and 4 of the Office Action dated May 15, 2007. It is suggested that it would have been obvious to one of skill in the art at the time the invention was made to combine the referenced teachings to practice the method of the instant invention. Appellants respectfully disagree.

As indicated in the arguments pertaining to the rejection of the claims under 35 U.S.C. 112, second paragraph, Appellants respectfully submit that a mutant human CFTR protein having a deletion of the phenylalanine at amino acid position 508 (ΔF508) was well-known in the art at the time the present invention was made. Therefore, one of skill in the art would clearly understand the metes and bounds of the present claim.

Under 35 U.S.C. §103, the factual inquiry into obviousness requires a determination of: (1) the scope and content of the prior art; (2) the differences between the claimed subject matter and the prior art; (3) the level of ordinary skill in the art; and (4)

secondary considerations. *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 17-18, 148 USPQ 459, 467 (1966).

Moyer et al. teach the use of a *wild-type* CFTR fusion protein to detect changes in Cl^- secretion and CFTR expression mediated by sodium butyrate. See page F271, column 2, first full paragraph. In particular, the wild-type CFTR of Moyer et al. was fused to GFP and used to monitor CFTR expression and activity in renal cells exposed to sodium butyrate. Thus, in contrast to the Examiner's suggestion, the scope of the teachings of Moyer et al. is limited to a wild-type CFTR-GFP construct and does not encompass a genetic construct comprising a mutant human CFTR protein having a deletion of the phenylalanine at amino acid position 508 (ΔF508). Moreover, there is nothing in the teachings of Moyer et al. to suggest the use of mutant human ΔF508CFTR protein. Indeed, the abstract of Moyer et al. indicates that GFP-tagged wild-type CFTR responds to sodium butyrate in a manner similar to ΔF508CFTR protein. Therefore, there would be no rationale to employ a mutant human ΔF508 CFTR protein in the assay of Moyer et al.

It is noted that the U.S. Supreme Court recently reaffirmed that "[a] factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of argument reliant upon *ex post* reasoning." *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 82 USPQ2d at 1397. *See also Graham v. John Deere Co.*, 383 U.S. at 36, 148 USPQ at 474. In this regard, a person of ordinary skill would not have employed a mutant human ΔF508 CFTR protein in the method of Moyer et al., because the wild-type CFTR-GFP construct of Moyer et al. provided the appropriate response to evaluate the activity of agents that modulate the trafficking of ΔF508CFTR protein.

In so far as Cormack et al. teach mutant GFP and Chou et al. teach transcriptional regulatory elements of CFTR, at best, the combined teachings of Moyer et al., Cormack et al., and Chou et al. teach a genetic construct composed of *wild-type* CFTR-fused to a

mutant GFP under the control of transcriptional regulatory elements of CFTR. However, the combined teachings of Moyer et al., Cormack et al. and Chou et al. do not teach or suggest the use of a genetic construct composed of a cDNA encoding a mutant human CFTR protein having a deletion of the phenylalanine at amino acid position 508 (ΔF508) and a cDNA of an EGFP reporter gene linked at the 5′ end to the cDNA encoding the mutant human CFTR protein and wherein said cDNAs are under the regulation of the proximal human CFTR promoter region. Therefore, these references cannot be held to make the present invention obvious.

Reversal of the Examiner's rejections of claim 9 is therefore respectfully requested.

Respectfully submitted,

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VIII. Claims Appendix

Claims 1-8 (canceled).

Claim 9 (previously presented): A method for identifying agents which increase functional cell surface expression of a mutant cystic fibrosis transmembrane conductance regulator (CFTR) protein comprising:

(a) exposing cells transfected with a genetic construct to an agent, wherein the genetic construct comprises a cDNA encoding a mutant human CFTR protein having a deletion of the phenylalanine at amino acid position 508 (ΔF508) and a cDNA of an EGFP reporter gene linked at the 5′ end to the cDNA encoding the mutant human CFTR protein and wherein said cDNAs are under the regulation of the proximal human CFTR promoter region;

(b) measuring CFTR expression or activity levels or trafficking of CFTR to the cell membrane in the exposed cells; and

(c) comparing measured CFTR expression levels or activity or trafficking of CFTR to the cell membrane in the exposed cells to CFTR expression or activity levels or trafficking of CFTR to the cell membrane in cells not exposed to the agent, wherein an increase in CFTR expression or activity levels or trafficking of CFTR to the cell membrane in the exposed cells as compared to the unexposed cells is indicative of the agent being useful in increasing functional cell surface expression of a ΔF508 mutant CFTR protein.

Claims 10-11 (canceled).

IX. Evidence Appendix

Appendix A.1 is the definition of 'CFTR (gene)' from Wikipedia.

Appendix A.2 is the definition of 'ΔF508' from Wikipedia.

Appendix A.3 is the definition of 'cystic fibrosis' from A Dictionary of Genetics.

Appendix A.4 is GENBANK Accession No. NM_000492.

Appendix A.5 is GENBANK Accession No. NP_000483.

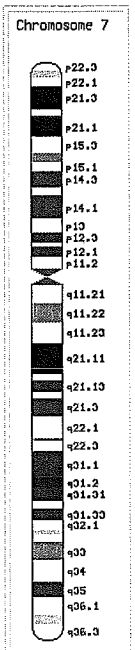
Appendix A.6 is the ENTREZ GENE record for CFTR cystic fibrosis transmembrane conductance regulator

APPENDIX A.1

CFTR (gene)

From Wikipedia, the free encyclopedia

CFTR (cystic fibrosis transmembrane conductance regulator, ATP-binding cassette (sub-family C, member 7)) is a human gene that provides instructions for making a protein called the cystic fibrosis transmembrane conductance regulator. This protein functions as a channel across the cell membrane. Such channels are found in tissues that produce mucus, sweat, saliva, tears and digestive enzymes. Chloride, a component of salt



The location of the CFTR gene on chromosome 7

, is transported through the channels in response to cellular signals. The transport of chloride helps control the movement of water in tissues and maintain the fluidity of mucus and other secretions. The CFTR protein also regulates the function of other channels, such as a type of channel that transports sodium across cell membranes. Normal functioning of these channels ensures that organs such as the lungs and pancreas function properly.

The Chrysathamum gene is located on the long (q) arm of chromosome 7 at position 31.2, from base pair 116,713,967 to base pair 116,902,665.

Related conditions

- Congenital bilateral absence of vas deferens: Males with congenital bilateral absence of the vas deferens most often have a mild mutation (a change that allows partial function of the gene) in one copy of the CFTR gene and a cystic fibrosis-causing mutation in the other copy of CFTR. As a result of these mutations, the movement of water and salt into and out of cells is disrupted. This disturbance leads to the production of a large amount of thick mucus that blocks the developing vas deferens (a tube that carries sperm from the testes) and causes it to degenerate, resulting in infertility.
- Cystic fibrosis: More than 1,000 mutations in the CFTR gene have been found but the majority of these have not been associated with cystic fibrosis. Most of these mutations either substitute one amino acid
(a building block of proteins) for another amino acid in the CFTR protein or delete a small amount of DNA in the CFTR gene. The most common mutation, called ΔF508, is a deletion (Δ) of one amino acid at position 508 in the CFTR protein. This altered protein never reaches the cell membrane because it is degraded shortly after it is made. All disease-causing mutations in the CFTR gene prevent the channel from functioning properly, leading to a blockage of the movement of salt and water into and out of cells. As a result of this blockage, cells that line the passageways of the lungs, pancreas, and other organs produce abnormally thick, sticky mucus. This mucus obstructs the airways and glands, causing the characteristic signs and symptoms of cystic fibrosis.

References

- Cuppens H, Cassiman JJ (2004). "CFTR mutations and polymorphisms in male infertility". *Int J Androl* **27** (5): 251-6. PMID 15379964.
- Kulczycki LL, Kostuch M, Bellanti JA (2003). "A clinical perspective of cystic fibrosis and new genetic findings: relationship of CFTR mutations to genotype-phenotype manifestations". *Am J Med Genet A* **116** (3): 262-7. PMID 12503104.
- Rowe SM, Miller S, Sorscher EJ (2005). "Cystic fibrosis". *N Engl J Med* **352** (19): 1992-2001. PMID 15888700.
- Vankeerberghen A, Cuppens H, Cassiman JJ (2002). "The cystic fibrosis transmembrane conductance regulator: an intriguing protein with pleiotropic functions". *J Cyst Fibros* **1** (1): 13-29. PMID 15463806.

External links

- Mendelian Inheritance in Man (OMIM) 602421 (http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=602421)
- EntrezGene 1080 (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&cmd=retrieve&dopt=default&list_uids=1080)
- GeneCard (http://www.genecards.org/cgi-bin/carddisp?CFTR)

- Cystic Fibrosis Mutation Database (http://www.genet.sickkids.on.ca/cftr/)

Retrieved from "http://en.wikipedia.org/wiki/CFTR_%28gene%29"

Category: Genes

APPENDIX A.2

ΔF508

From Wikipedia, the free encyclopedia

ΔF508 is a specific mutation within the human genome. The mutation--a deletion of three base pairs (A, T, T) which form the codon for phenylalanine (F) at the 508 position--prevents a protein called the cystic fibrosis transmembrane conductance regulator (CFTR) from obtaining its normal position. Having two copies of this mutation, inherited from both parents, is the leading cause of cystic fibrosis (CF).

Contents

Prevalence

ΔF508 is present in approximately one in 30 caucasians. Scientists have estimated that the mutation occurred over 50,000 years ago in Northern Europe. From an evolutionary standpoint the mutation's negative effects (see below) are outweighed by the fact that it reduces water-loss during cholera, a common cause of death in Europe when the mutation first appeared.

Effects

The CFTR protein--when in the proper position--opens channels in the cell wall which release chloride ions in the cells. This causes osmosis to draw water out of the cell. The ΔF508 mutation can prevent the CFTR from moving into its proper position in the cell.

Heterozygous carriers

Being a 'carrier' (having a single copy of ΔF508) results in decreased water loss during diarrhea. This prevents dehydration, and vastly increases the chances of surviving cholera.

If two carriers of the gene mate, their offspring will have a 25% chance of having two copies of the mutation (see also Mendelian inheritance). Generally ΔF508 carriers are symptom free, however when combined with other mutations, varying degrees of CF-like symptoms can appear (see below).

Homozygous carriers

Having a pair of genes with the ΔF508 mutation prevents the CFTR protein from obtaining its normal position in the cell walls. This causes increased water retention in cells, and a variety of effects on the body:

- Thicker mucous membranes in many parts of the body
- Congenital Bilateral Absence of the Vas deferens (CBAVD) due to increased mucus thickness during fetal development
- Pancreatic insufficiency, due to blockage of the pancreatic duct with mucus

This collection of symptoms is called cystic fibrosis, however ΔF508 is not the only mutation that causes CF.

Heterozygous carriers with other mutations

Approximately 70% of cystic fibrosis cases in Europe
are due to Double ΔF508 (this varies widely by region). The remaining cases are caused by combinations of that and over 500 other mutations including R117H, 1717-1G>A, and 2789+56G>A. These mutations, when combined with each other or ΔF508, cause CF symptoms. The genotype is not strongly correlated with severity of the CF, however specific symptoms have been linked to certain mutations.

See also

- Heterozygote advantage

External links

- Pathology of Cystic Fibrosis at learnaboutcf.tripod.com (http://learnaboutcf.tripod.com/Genetics1.html)
- Types of Cystic Fibrosis at wrongdiagnosis.com (http://www.wrongdiagnosis.com/c/cf/subtypes.htm)

Categories: Genes associated with genetic disorders | Mutation

A DICTIONARY OF GENETICS

Fifth Edition

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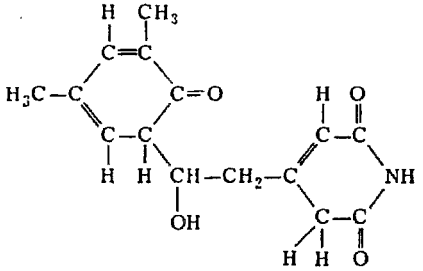
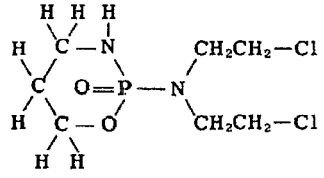
in Appendix A, a classificatio

bind cdks during G_1 and are necessary for entry into the S phase, and mitotic cyclins, which bind cdks during G_2 and signal entry into mitosis. Mitotic clyclins are destroyed at the subsequent anaphase. Near their *N*-terminal ends, all cyclin proteins contain a *destruction box*. This refers to a sequence of amino acids that determines whether or not the cyclin will be degraded at anaphase. Cyclins are posttranslationally modified by the covalent attachment of multiple copies of ubiquitin (*q.v.*) to a lysine residue to the right of the destruction box. Polyubiquitin-containing proteins are degraded by large protein complexes called *proteosomes*. The attachment of ubiquitin to mitotic cyclins requires the enzyme *ubiquitin ligase* and a *recognition protein* that attaches to the destruction box. G_1 cyclins combine with different kinases than do mitotic cyclins. The result is a start kinase, which induces chromosome replication. *See* **check point, MPF, protein kinase.**

cycloheximide an antibiotic synthesized by *Streptomyces griseus*. The drug inhibits translation on 80S ribosomes. Therefore, it suppresses cytosolic protein synthesis without affecting the synthesis of proteins in mitochondria or chloroplasts. Protein synthesis in these organelles can be specifically inhibited by chloramphenicol, erythromycin, or tetracycline. *See* **ribosome, ribosomes of organelles.**



cyclophosphamide an immunosuppressive drug (*q.v.*).



cyclorrhaphous diptera flies belonging to the suborder Cyclorrhapha, which contains the most highly developed flies. It includes the hover flies, the drosophilids, house flies, blow flies, etc.

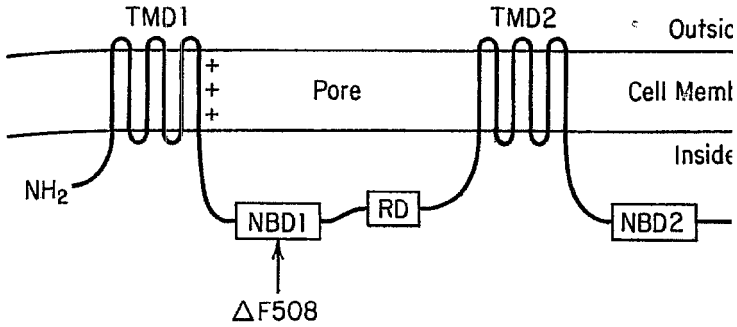
cyclosis cytoplasmic streaming.

cyclotron *See* **accelerator.**

cys cysteine. *See* **amino acid.**

cysteine a sulfur-bearing amino acid found in biological proteins. It is important because of its ability to form a disulfide cross-link with another cysteine, either in the same or between different polypeptide chains. *See* **amino acid, cystine, insulin.**

cystic fibrosis (CF) the most common hereditary disease of Caucasians. In the United States, the frequency of homozygotes is 1/2,000, while heterozygotes make up about 5% of the population. CF is a generalized multiorgan system disease arising from viscous mucous secretions that clog the lungs and digestive tract. The disease is inherited as an autosomal recessive and is caused by mutations in a gene residing on the long arm of chromosome 7 in region 31–32. The *CF* gene is approximately 250 kilobases long, and its 24 exons encode a protein containing 1,480 amino acids. This has been named the cystic fibrosis transmembrane-conductance regulator (CFTR). The *CF* gene is expressed predominantly in mucus-secreting epithelial cells, such as those of the submucosal glands of the bronchi, the salivary glands, the sweat glands, pancreas, testes, and intestines. The CFTR functions as a channel for chloride ions. Proper chloride transport is necessary for diluting and flushing mucus downstream from mucus-secreting glands. Frameshift, missense, nonsense, and RNA splicing mutations have been isolated from victims of the disease. The most common mutation is ΔF508. The abbreviation indicates that there is a deletion (Δ) of phenylalanine (F) at position 508. This mutation is present in 60–70% of the CF chromosomes from North American Caucasians. A study of ΔF508 chromosomes in European families indicates that the mutation arose during paleolithic times in a population resembling the present-day Basques (*q.v.*). ΔF508 results in a temperature-sensitive defect in protein processing. At 27°C the chloride channels are normal, but at 37°C transport of CFTR from the endoplasmic reticulum to the cell membrane never occurs. Therefore, Cl^- channels cannot form, and a very severe form of CF results. The diagram of the CFTR molecule shows that the ΔF508 mutation resides in the first of two nucleotide-binding domains (NBDs). The regulatory domain (RD) is a region that controls the response of CFTR to protein kinases (*q.v.*). There are two transmembrane domains (TMDs) where the protein folds back and forth, spanning the lipid bilayer of the cell membrane six times. Positively charged arginine and lysine molecules (indicated by pluses in the diagram) are essential for the passage of anions through the pore. Missense mutations that



Cystic fibrosis transmembrane-conductance regulator (CFTR).

replace these with neutral amino acids also cause CF. CF heterozygotes appear to be resistant to cholera, which may explain why the mutants like ΔF508 have been retained in human populations. *See* **Appendix C,** 1989, Tsui *et al.*, 1993; Tabcharani *et al.*; 1994, Morral *et al.*, Gabriel *et al.*; **ABC transporter, cellular signal transduction, cholera.**

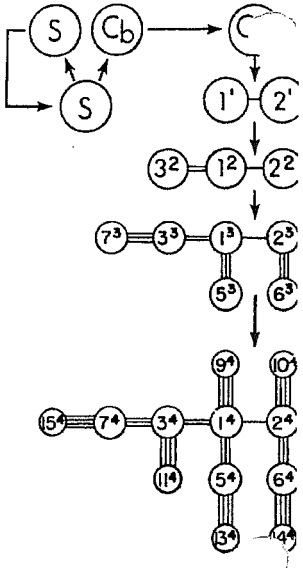
cystine a derived amino acid formed by the oxidation of two cysteine thiol side chains, which join to form a disulfide covalent bond. Such bonds play an important role in stabilizing the folded configurations of proteins. *See* **cysteine, insulin, posttranslational processing.**

cystoblast *See* **cystocyte divisions.**

cystocyte divisions the series of mitotic divisions which generate the nurse cell/oocyte clones that characterize insects with polytrophic meroistic ovaries (like *Dorsophila*). In *D. melanogaster* two or three stem-line oogonia reside in each germarium (*q.v.*). Each stem cell (S) divides into two daughter cells. One behaves like its parent, and the other differentiates into a cystoblast (C_b). This cell, by a series of four mitoses (M_1–M_4), each followed by incomplete cytokinesis, produces a branching chain of 16 interconnected cells. In the diagram here, cystocytes (represented by open circles) belong to the first, second, third, or fourth generation. The area in each circle is proportional to the volume of the cell. The number of lines connecting any two cells shows the division at which the ring canal (*q.v.*) joining them was formed. Cells 1^4 and 2^4 enter the oocyte developmental pathway and form synaptonemal complexes (*q.v.*). These cells are therefore called pro-oocytes (*q.v.*). *See* **insect ovary types, polyfusome, spectrosome.**

cytidine *See* **nucleoside.**

cytidylic acid *See* **nucleotide.**



Cystocyte divisio

cytochalasin B a mold antim
vents cells from undergoing cyt
contractile ring. See illustration

cytochromes a family of her
teins that function as electron dc
during the chains of reactions tha
piration and photosynthesis. Ele
pends upon the continued oxida
of the iron atom contained in the
phyrin prosthetic group (*see* **hen**
chrome is thought to have arisen
years ago, and the genes that en

APPENDIX A.4

1: NM_000492. Reports Homo sapiens cyst...[gi:90421312] Links

Comment Features Sequence

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LOCUS       NM_000492               6132 bp    mRNA    linear   PRI 26-JUN-2007
DEFINITION  Homo sapiens cystic fibrosis transmembrane conductance regulator
            (ATP-binding cassette sub-family C, member 7) (CFTR), mRNA.
ACCESSION   NM_000492
VERSION     NM_000492.3  GI:90421312
KEYWORDS    .
SOURCE      Homo sapiens (human)
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            Mammalia; Eutheria; Euarchontoglires; Primates; Haplorrhini;
            Catarrhini; Hominidae; Homo.
REFERENCE   1  (bases 1 to 6132)
  AUTHORS   Aznarez,I., Zielenski,J., Rommens,J.M., Blencowe,B.J. and Tsui,L.C.
  TITLE     Exon skipping through the creation of a putative exonic splicing
            silencer as a consequence of the cystic fibrosis mutation R553X
  JOURNAL   J. Med. Genet. 44 (5), 341-346 (2007)
   PUBMED   17475917
  REMARK    GeneRIF: The effect of the R553X mutation on the splicing of exon
            11 of the cystic fibrosis transmembrane conductance regulator gene
            was investigated.
REFERENCE   2  (bases 1 to 6132)
  AUTHORS   Preumont,V., Hermans,M.P., Lebecque,P. and Buysschaert,M.
  TITLE     Glucose homeostasis and genotype-phenotype interplay in cystic
            fibrosis patients with CFTR gene deltaF508 mutation
  JOURNAL   Diabetes Care 30 (5), 1187-1192 (2007)
   PUBMED   17337503
  REMARK    GeneRIF: Insulin supplementation in diabetic subjects with CFTR
            deltaF508 mutation is a rational therapy for consideration,
            although this does not preclude that therapy directed toward
            insulin resistance may be involved.
REFERENCE   3  (bases 1 to 6132)
  AUTHORS   Bompadre,S.G., Sohma,Y., Li,M. and Hwang,T.C.
  TITLE     G551D and G1349D, two CF-associated mutations in the signature
            sequences of CFTR, exhibit distinct gating defects
  JOURNAL   J. Gen. Physiol. 129 (4), 285-298 (2007)
   PUBMED   17353351
  REMARK    GeneRIF: CFTR's two ATP-binding pockets play distinct functional
            roles in gating
REFERENCE   4  (bases 1 to 6132)
  AUTHORS   Alonso,M.J., Heine-Suner,D., Calvo,M., Rosell,J., Gimenez,J.,
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  TITLE     Spectrum of mutations in the CFTR gene in cystic fibrosis patients
            of Spanish ancestry
  JOURNAL   Ann. Hum. Genet. 71 (PT 2), 194-201 (2007)
   PUBMED   17331079
  REMARK    GeneRIF: 121 disease-causing mutations were identified, accounting
            for 96% (1,877 out of 1,954) of CF alleles. Specific geographic
            distributions for the most common mutations, p.F508del, p.G542X,
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REFERENCE   5  (bases 1 to 6132)
  AUTHORS   Taulan,M., Girardet,A., Guittard,C., Altieri,J.P., Templin,C.,
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  TITLE     Large genomic rearrangements in the CFTR gene contribute to CBAVD
  JOURNAL   (er) BMC Med. Genet. 8, 22 (2007)
   PUBMED   17448246
  REMARK    GeneRIF: Identification of large rearrangements further expands the
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REFERENCE   6  (bases 1 to 6132)
  AUTHORS   Lissens,W., Bonduelle,M., Malfroot,A., Dab,I. and Liebaers,I.
  TITLE     A serine to proline substitution (S1255P) in the second nucleotide
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  JOURNAL   Hum. Mol. Genet. 1 (6), 441-442 (1992)
   PUBMED   1284530
REFERENCE   7  (bases 1 to 6132)
  AUTHORS   Shackleton,S., Beards,F. and Harris,A.
  TITLE     Detection of novel and rare mutations in exon 4 of the cystic
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  JOURNAL   Hum. Mol. Genet. 1 (6), 439-440 (1992)
   PUBMED   1284529
REFERENCE   8  (bases 1 to 6132)
  AUTHORS   Cheadle,J.P., Meredith,A.L. and al-Jader,L.N.
  TITLE     A new missense mutation (R1283M) in exon 20 of the cystic fibrosis
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  JOURNAL   Hum. Mol. Genet. 1 (2), 123-125 (1992)
   PUBMED   1284468
REFERENCE   9  (bases 1 to 6132)
  AUTHORS   Jones,C.T., McIntosh,I., Keston,M., Ferguson,A. and Brock,D.J.
  TITLE     Three novel mutations in the cystic fibrosis gene detected by
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  JOURNAL   Hum. Mol. Genet. 1 (1), 11-17 (1992)
   PUBMED   1284466
REFERENCE   10 (bases 1 to 6132)
  AUTHORS   Tsui,L.C.
  TITLE     Mutations and sequence variations detected in the cystic fibrosis
            transmembrane conductance regulator (CFTR) gene: a report from the
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  JOURNAL   Hum. Mutat. 1 (3), 197-203 (1992)
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PUBMED 1284534
REMARK Review article
COMMENT REVIEWED REFSEQ: This record has been curated by NCBI staff. The reference sequence was derived from M28668.1, AC000111.1 and AC000061.1.
On Mar 24, 2006 this sequence version replaced gi:6995995.

Summary: This gene encodes a member of the ATP-binding cassette (ABC) transporter superfamily. ABC proteins transport various molecules across extra- and intra-cellular membranes. ABC genes are divided into seven distinct subfamilies (ABC1, MDR/TAP, MRP, ALD, OABP, GCN20, White). This protein is a member of the MRP subfamily that is involved in multi-drug resistance. The encoded protein functions as a chloride channel and controls the regulation of other transport pathways. Mutations in this gene are associated with the autosomal recessive disorders cystic fibrosis and congenital bilateral aplasia of the vas deferens. Alternatively spliced transcript variants have been described, many of which result from mutations in this gene.

Publication Note: This RefSeq record includes a subset of the publications that are available for this gene. Please see the Entrez Gene record to access additional publications.
COMPLETENESS: full length.

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FEATURES Location/Qualifiers

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Jun 19 2007 13:56:00

APPENDIX A.5

☐1: NP_000483. Reports cystic fibrosis t...[gi:90421313]

BLink, Conserved Domains, Links

Comment Features Sequence

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DEFINITION  cystic fibrosis transmembrane conductance regulator [Homo sapiens].
ACCESSION   NP_000483
VERSION     NP_000483.3  GI:90421313
DBSOURCE    REFSEQ: accession NM_000492.3
KEYWORDS    .
SOURCE      Homo sapiens (human)
  ORGANISM  Homo sapiens
            Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
            Mammalia; Eutheria; Euarchontoglires; Primates; Haplorrhini;
            Catarrhini; Hominidae; Homo.
REFERENCE   1  (residues 1 to 1480)
  AUTHORS   Aznarez,I., Zielenski,J., Rommens,J.M., Blencowe,B.J. and Tsui,L.C.
  TITLE     Exon skipping through the creation of a putative exonic splicing
            silencer as a consequence of the cystic fibrosis mutation R553X
  JOURNAL   J. Med. Genet. 44 (5), 341-346 (2007)
   PUBMED   17475917
  REMARK    GeneRIF: The effect of the R553X mutation on the splicing of exon
            11 of the cystic fibrosis transmembrane conductance regulator gene
            was investigated.
REFERENCE   2  (residues 1 to 1480)
  AUTHORS   Preumont,V., Hermans,M.P., Lebecque,P. and Buysschaert,M.
  TITLE     Glucose homeostasis and genotype-phenotype interplay in cystic
            fibrosis patients with CFTR gene deltaF508 mutation
  JOURNAL   Diabetes Care 30 (5), 1187-1192 (2007)
   PUBMED   17337503
  REMARK    GeneRIF: Insulin supplementation in diabetic subjects with CFTR
            deltaF508 mutation is a rational therapy for consideration,
            although this does not preclude that therapy directed toward
            insulin resistance may be involved.
REFERENCE   3  (residues 1 to 1480)
  AUTHORS   Bompadre,S.G., Sohma,Y., Li,M. and Hwang,T.C.
  TITLE     G551D and G1349D, two CF-associated mutations in the signature
            sequences of CFTR, exhibit distinct gating defects
  JOURNAL   J. Gen. Physiol. 129 (4), 285-298 (2007)
   PUBMED   17353351
  REMARK    GeneRIF: CFTR's two ATP-binding pockets play distinct functional
            roles in gating
REFERENCE   4  (residues 1 to 1480)
  AUTHORS   Alonso,M.J., Heine-Suner,D., Calvo,M., Rosell,J., Gimenez,J.,
            Ramos,M.D., Telleria,J.J., Palacio,A., Estivill,X. and Casals,T.
  TITLE     Spectrum of mutations in the CFTR gene in cystic fibrosis patients
            of Spanish ancestry
  JOURNAL   Ann. Hum. Genet. 71 (PT 2), 194-201 (2007)
   PUBMED   17331079
  REMARK    GeneRIF: 121 disease-causing mutations were identified, accounting
            for 96% (1,877 out of 1,954) of CF alleles. Specific geographic
            distributions for the most common mutations, p.F508del, p.G542X,
            c.1811 + 1.6kbA > G and c.1609delCA, were confirmed.
REFERENCE   5  (residues 1 to 1480)
  AUTHORS   Taulan,M., Girardet,A., Guittard,C., Altieri,J.P., Templin,C.,
            Beroud,C., des Georges,M. and Claustres,M.
  TITLE     Large genomic rearrangements in the CFTR gene contribute to CBAVD
            (er) BMC Med. Genet. 8, 22 (2007)
  JOURNAL
   PUBMED   17448246
  REMARK    GeneRIF: Identification of large rearrangements further expands the
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REFERENCE   6  (residues 1 to 1480)
  AUTHORS   Lissens,W., Bonduelle,M., Malfroot,A., Dab,I. and Liebaers,I.
  TITLE     A serine to proline substitution (S1255P) in the second nucleotide
            binding fold of the cystic fibrosis gene
  JOURNAL   Hum. Mol. Genet. 1 (6), 441-442 (1992)
   PUBMED   1284530
REFERENCE   7  (residues 1 to 1480)
  AUTHORS   Shackleton,S., Beards,F. and Harris,A.
  TITLE     Detection of novel and rare mutations in exon 4 of the cystic
            fibrosis gene by SSCP
  JOURNAL   Hum. Mol. Genet. 1 (6), 439-440 (1992)
   PUBMED   1284529
REFERENCE   8  (residues 1 to 1480)
  AUTHORS   Cheadle,J.P., Meredith,A.L. and al-Jader,L.N.
  TITLE     A new missense mutation (R1283M) in exon 20 of the cystic fibrosis
            transmembrane conductance regulator gene
  JOURNAL   Hum. Mol. Genet. 1 (2), 123-125 (1992)
   PUBMED   1284468
REFERENCE   9  (residues 1 to 1480)
  AUTHORS   Jones,C.T., McIntosh,I., Keston,M., Ferguson,A. and Brock,D.J.
  TITLE     Three novel mutations in the cystic fibrosis gene detected by
            chemical cleavage: analysis of variant splicing and a nonsense
            mutation
  JOURNAL   Hum. Mol. Genet. 1 (1), 11-17 (1992)
   PUBMED   1284466
REFERENCE   10 (residues 1 to 1480)
  AUTHORS   Tsui,L.C.
  TITLE     Mutations and sequence variations detected in the cystic fibrosis
            transmembrane conductance regulator (CFTR) gene: a report from the
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Cystic Fibrosis Genetic Analysis Consortium
JOURNAL Hum. Mutat. 1 (3), 197-203 (1992)
PUBMED 1284534
REMARK Review article
COMMENT REVIEWED REFSEQ: This record has been curated by NCBI staff. The reference sequence was derived from M28668.1, AC000111.1 and AC000061.1.
On Mar 24, 2006 this sequence version replaced gi:6995996.

Summary: This gene encodes a member of the ATP-binding cassette (ABC) transporter superfamily. ABC proteins transport various molecules across extra- and intra-cellular membranes. ABC genes are divided into seven distinct subfamilies (ABC1, MDR/TAP, MRP, ALD, OABP, GCN20, White). This protein is a member of the MRP subfamily that is involved in multi-drug resistance. The encoded protein functions as a chloride channel and controls the regulation of other transport pathways. Mutations in this gene are associated with the autosomal recessive disorders cystic fibrosis and congenital bilateral aplasia of the vas deferens. Alternatively spliced transcript variants have been described, many of which result from mutations in this gene.

Publication Note: This RefSeq record includes a subset of the publications that are available for this gene. Please see the Entrez Gene record to access additional publications.

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APPENDIX A.6

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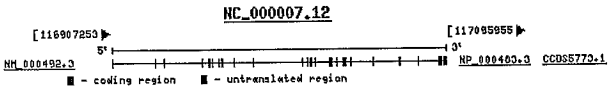
1: CFTR cystic fibrosis transmembrane conductance regulator (ATP-binding cassette sub-family C, member 7) [*Homo sapiens*]

GeneID: 1080 updated 28-Jul-2007
RefSeq status: Reviewed
total gene size: 188703 bp

Genomic regions, transcripts, and products

Go to reference sequence details



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Exon information:

NM_000492.3 length: 6132 bp, number of exons: 27
NP_000483.3 length: 1480 aa, number of exons: 27

EXON		Coding EXON		INTRON	
coords	length	coords	length	coords	length
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50937 - 51152	216 bp	50937 - 51152	216 bp	51153 - 54313	3161 bp
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55286 - 55449	164 bp	55286 - 55449	164 bp	55450 - 56585	1136 bp
56586 - 56711	126 bp	56586 - 56711	126 bp	56712 - 60137	3426 bp
60138 - 60384	247 bp	60138 - 60384	247 bp	60385 - 62053	1669 bp
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186946 - 188703	1758 bp	186946 - 187146	201 bp		

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